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(54) **Anti-ulcer pharmaceutical compositions containing salicylic acid or its salts**

(57) The invention relates to new anti-ulcer and anti-ulcer/antiinflammatory compositions and products, which contain an anti-ulcer agent or a salt thereof and salicylic acid or an alkali metal salt thereof optionally together with a non-steroidal antiinflammatory agent. As an anti-ulcer agent preferably cimetidine or ranitidine is employed, while the preferred non-steroidal antiinflammatory agent is indomethacin.

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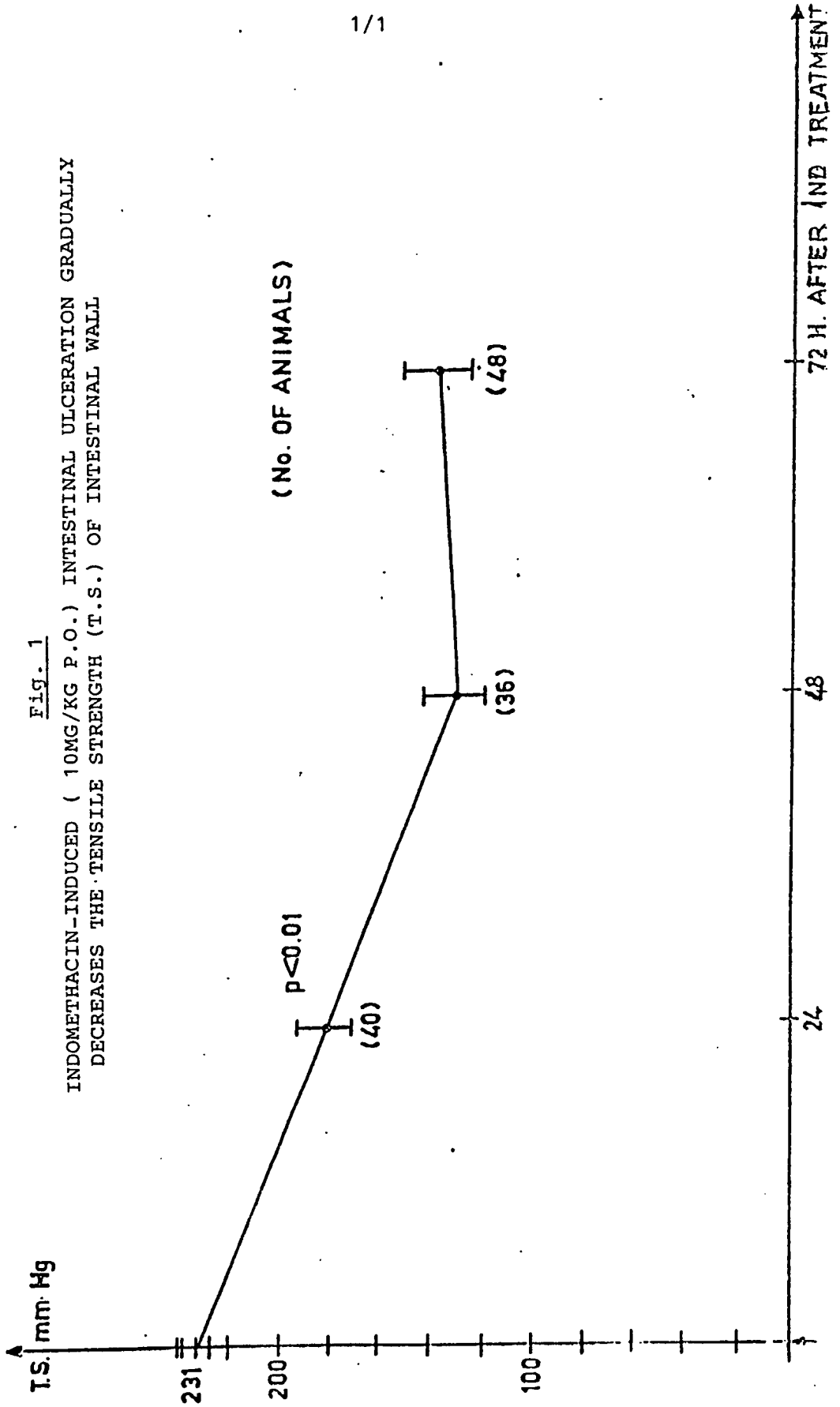
Fig. 1

INDOMETHACIN-INDUCED (10MG/KG P.O.) INTESTINAL ULCERATION GRADUALLY DECREASES THE TENSILE STRENGTH (T.S.) OF INTESTINAL WALL



SPECIFICATION

Anti-ulcer pharmaceutical compositions

The invention relates to new anti-ulcer pharmaceutical compositions and a process for their preparation. More particularly, the invention concerns new pharmaceutical compositions containing two or more active ingredients which compositions are effective against gastrointestinal ulceration and, if desired, may also contain anti-inflammatory agents.

Since the H_2-receptor antagonists were first described, [Nature *236*, 385 (1962)] this novel group of anti-ulcer agents has been subjected to extensive experimental and clinical investigations. Shortly afterwards, cimetidine (N"-cyano-N'-methly-N-[2-(((5-methyl-1H-imidazolyl-4-yl)-methyl)-thio)-ethyl]-guanidine) appeared on the market and has been favourably received. In the past few years numerous new H_2-receptor antagonists have been prepared and investigated.

During the last few years, since the world-wide introduction of cimetidine, more than 1500 articles have been published concerning this agent. In experiments on rats it has been demonstrated for example by P. Del Soldato et al [Br. J. Pharmac. *67*, 33 (1979)] that cimetidine cannot prevent indomethacin-induced intestinal ulceration. Similar observations have recently been published by W.S. Mitchell et al [Brit. Med. J. *284*, 731 (1982)] following human clinical practice. It has been reported that the concurrent administration of cimetidine and indomethacin has resulted in perforated ulcers in the case of several patients.

It is well known that gastrointestinal ulcers, a typical disease peculiar to civilized communities, are occurring in more and more people. Among ulcerous patients there are numerous people suffering also from inflammatory or degenerative locomotor diseases. In such cases the medical attendant has to face a hitherto practically insoluble situation since until now no pharmaceutical composition was known in the art which could effectively be used under these conditions without serious side-effects. It is highly probable that the concurrent administration of an anti-ulcer agent and a non-steroidal antiinflammatory agent may accelerate the perforation of the ulcer.

It would thus be desirable to be able to provide a pharmaceutical composition which is devoid of these disadvantages and in which the activity of the anti-ulcer active ingredient is favourably increased, i.e. potentiated.

It is known that a common, undesired side-effect of non-steroidal antiinflammatory agents is their ulcerogenic effect. According to numerous publications 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-yl-acetic acid (indomethacin), 4-butyl-1,2-diphenylpyrazolidine-3,5-dione (phenylbutazone), d-2-(6-methoxy-2-naphthyl)-propionic acid (naproxen), 3-(3-trifluoromethylanilino)-nicotinic acid (niflumic acid) and acetyl salicylic acid show an ulcerogenic side-effect. There are several methods by which the above undesired side-effect of antiinflammatory substances can be reduced. Our own experiments have showed that some reduction of side-effects can be achieved using certain salicylates (British Patent Specification 1,483,165) but there is no suggestion in the literature to combine these agents as anti-ulcer active ingredients; on the contrary, it is generally pointed out that the salicylates have an undesirable effect on the gastrointestinal condition (see for example: Aspirin and Related Drugs: Their Actions and Uses, K.D. Rainsford, K. Brune, M.W. Whitehouse, Birkhäuser Verlag, Basel und Stuttgart *1977*). Though different pharmacological investigations, recently carried out, have demonstrated unambiguously that sodium salicyate has a gastrointestinal cytoprotective effect (e.g. J. Pharm. Pharmac. *28*, 655 1976); Prostaglandins *21*, Suppl. 139 (1981)), it has also been reported that the gastrointestinal cytoprotective effect of sodium salicylate has no connection with gastric acid secretion (Adv. Physiol. Sci., Vol. 29, Gastrointestinal Defense Mechanisms, Pergamon Press - Akadémiai Kiadó, Budapest, Hungary, 1981).

We have found that in a concurrent administration of various antiinflammatory agents, particularly indomethacin, and cimetidine, the latter compound in a certain concentration range does not inhibit the intestinal ulcerogenic effect of the antiinflammatory agents, instead it facilitates this undesired action. Accordingly, it could not be expected that the administration of a certain dose of salicylic acid or a salicylate as a further component would almost entirely suppress the undesired side-effect.

The present invention is based on the surprising discovery that a combination of known anti-ulcer agents with sodium salicylate has a more significant, i.e. synergistic, anti-ulcer effect than the anti-ulcer agent alone. We have further found that when a non-steroidal antiinflammatory agent is added to such a combination, the undesired side-effects of the non-steroidal antiinflammatory agent can also be avoided.

According to one feature of the invention there are provided compositions comprising, as active ingredient, 1 part by weight of an anti-ulcer agent or a salt thereof and 0.1 to 10 parts by weight of salicylic acid or an alkali metal salt thereof. In one particular embodiment the active ingredient further includes 0.01 to 1 part by weight of a non-steroidal antiinflammatory agent or a salt thereof. If desired, the compositions may also contain carriers and/or other additives such as are conveniently used in the pharmaceutical industry.

According to a preferred embodiment of the invention there are provided compositions wherein the anti-ulcer agent comprises cimetidine, ranitidine (N-[2-(((5-(dimethylamino)-methyl-2-furanyl)-methyl)-thio)-ethyl]-N'-methyl-2-nitro-1,1-ethylenediamine), propantheline (N,N-diisopropyl-N-methyl-2-(xanthene-9-carbonyloxy)-ethylammonium hydroxide), gastrixone (xanthene-9-carboxylic acid tropinester methyl hydrochloride) or zolimidine (2-(*p*-methylsulfonylphenyl)-imidazo[1,2-*a*]-pyridine).

According to a further preferred embodiment of the invention the pharmaceutical compositions contain, as a non-steroidal antiinflammatory agent, indomethacin, naproxen, phenylbutazone, acetylsalicilic acid or niflumic acid.

A preferred composition according to the invention may for example contain 0.1 to 1 part by weight of sodium salicylate, 1 part by weight of cimetidine and optionally 0.01 to 1 part by weight of indomethacin. Also preferred are compositions of 0.01 to 1 part by weight of sodium salicylate and 1 part by weight of cimetidine. The above compositions may additionally contain one or more conventional carriers and/or other additives.

In the compositions according to the invention the total active ingredient concentration preferably constitutes from 10 to 90% by weight of the total weight of the composition, the remainder consisting of carriers and/or other additives.

The invention further relates to a process for the preparation of these pharmaceutical compositions, which comprises mixing 0.1 to 10 parts by weight of salicylic acid or an alkali metal salt thereof with 1 part by weight of an anti-ulcer agent or a salt thereof, optionally together with 0.01 to 1 part by weight of a non-steroidal antiinflammatory agent and/or with carriers and/or with other additives.

According to a preferred embodiment of the process 1 part by weight of cimetidine is mixed with 0.1 to 1 part by weight of sodium salicylate optionally together with one or more conventional carriers and/or additives; or 0.1 to 1 part by weight of sodium salicylate and 0.1 to 1 part by weight of indomethacin are mixed with 1 part by weight of cimetidine optionally together with one or more conventional carriers and/or other additives; or 1 part by weight of ranitidine is mixed with 0.1 to 10 parts by weight of sodium salicylate optionally together with one or more conventional carriers and/or other additives.

According to a further aspect of the present invention there is provided a pharmaceutical product comprising a first container containing salicyclic acid or an alkali metal salt thereof and a second container containing an anti-ulcer agent or a salt thereof in association with written or printed directions to administer the contents of the first and second containers concurrently in an amount of 0.1 to 10 parts by weight of salicyclic acid or salt thereof to 1 part by weight of anti-ulcer agent or salt thereof. If desired the product may further include a non-steroidal antiinflammatory agent such as described hereinabove in which case the directions will further indicate that the non-steroidal antiinflammatory agent be administered concurrently with the contents of the first and second containers in an amount of 0.01 to 1 part by weight of non-steroidal antiinflammatory agent to 1 part by weight of anti-ulcer agent or salt thereof. The anti-ulcer agent or salt thereof and the salicylic acid or alkali metal salt thereof, together with, if present, the antiinflammatory agent and/or any carriers and/or other additives, may either be admixed prior to administration or alternatively they may be administered to the patient immediately concurrently e.g. as tablets taken one after the other.

EXPERIMENTAL METHODS

1) *Indomethacin-induced intestinal ulceration*

Non-fasted Hannover-Wistar rats, each weighing 120-150 g., were given a 15 mg./kg. dose of indomethacin in a Tween 80 suspension to induce fatal intestinal ulceration. The test material was administered immediately after the indomethacin treatment, also orally.

To evaluate the development of small intestinal ulcers, the tensile strength of the intestinal wall was determined by the so-called inflation technique [J. Pharm. Pharmac. *27*, 867 (1975)], because the erosion caused by ulcerogenesis leads to a weakening of the strength of the intestinal wall. The animals were killed 48 and 72 hours, respectively, after the indomethacin treatment by ether narcosis. The small intestine from pylorus to caecum was carefully removed and one end was ligated, while the other end was connected to a W+W electronic BP Recorder 8005 (Ugo Basile, Italy) through a polyethylene tube. The entire small intestine was placed into a physiological saline solution at 37°C and the pressure increased until air bubbles appeared at the weakened sites in the intestinal wall. This pressure, expressed in mmHg, is defined as the tensile strength (T.S.). Parallel with the progress of the indomethacin-induced intestinal ulceration the tensile strength of the intestinal wall, also called intestinal wall resistancy, gradually decreases as illustrated in Figure 1 of the accompanying drawings.

2) *Abs. alcohol-induced gastric necrosis*

Gastric necrosis was induced by acidic-alcohol, by the modified method of Robert et al. [Gastroenterology *77*, 433 (1979)]. Female Hannover-Wistar rats, each weighing 120-150 g., were fasted for 24 hours. Water was allowed *ad libitum*.

Compounds to be tested were administered orally 30 minutes prior to acidic-alcohol administration. Acidic-alcohol (cc. HCl:abs.ethanol=1:50 v/v) was administered orally through a canula in a dose of 0.5 ml. pro 100 g. of body weight. Two hours later the animals were killed by ether overdose. Stomachs were removed and opened along the major curvature. The lesions induced by ethanol are located at the corpus of the stomach as multiple linear hemorrhagic bands of necrotic tissue. Lengths of the lesions were measured and expressed in mm.-s and the total length of lesions of each stomach was calculated. Degree of lesion severity was expressed as the mean of total lesion-length per stomach. The stomach cytoprotection was expressed in comparison with the control animals.

3) *Gastric acid secretion in Shay-rats*

The tests were carried out according to the method of Shay et al. [Gastroenterology *5*, 43-46 (1945)]. Female Wistar rats, each weighing 120-150 g., were used. Pyrolic ligation was performed under ether anaesthesia after twenty-four hours' fasting. The animals were treated by the compounds to be tested intraperitoneally, immediately after the surgical intervention. The oral treatments were performed 30 minutes prior to operation. The animals were killed 4 hours after pyrolic ligation. After extension of the stomach the volume of gastric juice was measured and HCl concentration was determined by titration against 0.01 N NaOh in the presence of phenolphtalein as indicator. The amount of acid was expressed in μmoles per 100 g. of body weight. The statistical evaluation of the results was performed by Student's test.

Evaluation of the experimental results

By the above experiments the optimal cimetidine/sodium salicylate ratio, by which the indomethacin-induced intestinal ulceration (10 mg./kg.) and the gastric-acid secretion on Shay-rats could be inhibited was determined.

TABLE 1

Inhibition of Indomethacin-induced intestinal ulceration after concurrent administration of combinations of Cimetidine-Sodium-Salicylate in different ratios

Treatment	*n*	*Dose mg./kg. p.o.*	*Tensile strength of s.intestine, 48 hours after treat. in mmHg*	*Resistance of intestinal wall in percent of untreated value*
Untreated	30	-	231 ± 4	100
Indomethacin(Ind.)	26	10	111 ± 10	48^{xx}
Cimetidine (Cim.)	9	100	227 ± 1	98
Ind. + Cim.	10	10+100	63 ± 11	27^{xx}
Ind.+Cim.+Na–Salicylate	10	10+/100+10/	157 ± 28	68^{x}
Ind.+Cim.+Na–Salicylate	10	10+/100+25/	158 ± 19	68^{x}
Ind.+Cim.+Na–Salicylate	10	10+/100+50/	213 ± 7	94^{x}

x_p < 0.01 compared with Ind.+Cim. group
xx_p < 0.01 compared with untreated group

TABLE 2

Inhibition of gastric acid secretion by cimetidine and various combinations of cimetidine with Na-Salicylate on Shay-rats

Treatment	*n*	*Dose mg./kg.*	*HCl/4 hours μmoles/100 g. bwt. ± S.E.M.*	*Inhibition of HCl-production in percent*
Control	10	-	457 ± 55	-
Cimetidine (Cimet.)	10	50	163 ± 41	65^{x}
Cimet. + Na-Salicylate	10	50 + 10	172 ± 32	63^{x}
Cimet. + Na-Salicylate	10	50 + 25	40 ± 28	93^{xx}
Cimet. + Na-Salicylate	10	50 + 50	150 ± 42	68^{x}

x_p < 0.01 compared with the control
xx_p < 0.01 compared with the cimetidine 50 mg./kg. group

TABLE 3

In an abs.alcohol-induced gastric necrosis test Na-Salicylate is cytoprotective even in combination with cimetidine

Treatment	*n*	*Dose mg./kg. p.o.*	*Cytoprotection in % of the combination*	*Remarks*
Na-Salicylate	10	4	35	$ED_{50} = 7.9$
Na-Salicylate	10	8	60[x]	EE_{50} by A. Robert 15 mg./kg. Prostaglandins
Na-Salicylate	10	16	58[x]	Suppl. 21. 1981.
Na-Salicylate	10	16	94[x]	p. 139-146
Cimetidine (Cim.)				
Cim. + Na-Salicylate	10	8 + 4	5	$ED_{50} = 30$
Cim. + Na-Salicylate	10	16 + 8	41[x]	this contains:
Cim. + Na-Salicylate	10	32 + 16	82[x]	10 mg. of sodium-salicylate
Cim. + Na-Salicylate	10	64 + 32	93[x]	

According to the literature cimetidine is not protective in this test (Hagel et al.: Gastroenterology, 82.No.5. Suppl. 2. 1078, 1982; Soldato P.Del: Boll. Chim. Farm. 120, No.11, 631-638. 1981)

[x] $x_p < 0.01$

TABLE 4

Intestinal ulceration after repeated treatment (on three consecutive days) with Indomethacin, Cimetidine and combination of Cimetidine and Na-Salicylate (2:1)

Treatment	*n*	*Dose mg./kg. p.o.*	*Tensile strength of s.intestine, 24 hours after last treat. in mmHg*	*Mortality in percent*	*Resistance of intestinal wall in percent of untreated value*
Untreated (normal)	30	-	231 ± 4	-	100
Indomethacin (Ind.)	10	3 × 10	20 ± 10	30	9
Cimetidine (Cim.)	10	3 × 100	186 ± 16	0	80
Ind. + Cim.	10	3 × (10+100)	9 ± 15	50	4
Ind. + Cim. + Na-Salicylate 2:1	10	3 × (10+100+50)	225 ± 6	0	97[x]

[x] $x_p < 0.01$ compared with Ind. group

TABLE 5

Inhibition of gastric acid secretion in pylorus-ligated rats by Cimetidine and combination of Cimetidine and Na-Salicylate (2:1) treatment

Treatment	*n*	*Dose mg./kg. i.p.*	*HCl output/4 hours µmol/100 g. bwt.*	*Inhibition of HCl output %*	*Remark*
Control	40	-	425 ± 23	-	
Sodium-Salicylate	5	25	420 ± 47	0	
Sodium-Salicylate	5	50	381 ± 75	11	
Cimetidine	10	15	378 ± 55	12	
Cimetidine	10	25	327 ± 50	33	ED_{50}=54.4
Cimetidine	10	50	259 ± 62	39	
Cimetidine	5	100	140 ± 38	67	

TABLE 6

Inhibition of gastric acid secretion in Shay-rats by treatment with a 2:1 combination of Cimetidine and Na-Salicylate

Treatment	*n*	*Dose mg./kg. i.p.*	*HCl output/4 hours µmol/100 g. bwt ± S.E.M.*	*HCl output inhibition in %*	*Remark*
Control	9	-	435 ± 36	-	
Cim. + Na-Salicylate	10	6 + 3	316 ± 45	28	
Cim. + Na-Salicylate	10	12 + 6	374 ± 40	14	
Cim. + Na-Salicylate	10	24 + 12	256 ± 36	48[x]	ED_{50} = 35.6, which contains: Cim. = 23.8 mg, Na-Salicylate = = 11.8 mg.
Cim. + Na-Salicylate	20	50 + 25	156 ± 18	64[x]	
Cim. + Na-Salicylate	5	64 + 32	0	100	

$x_p < 0.01$ compared with the control

TABLE 7

Inhibition of Indomethacin-induced fatal intestinal ulceration after concurrent administration of various anti-ulcer compounds

Treatment	*n*	*Dose mg./kg. p.o.*	*Tensile strength of s.intestine, 72 hours after treat. in mmHg*	*Resistance of intestinal wall in % of untreated value*	*Mortality in percent*
Untreated	30	-	231 ± 4	100	-
Indomethacin (Ind.)	26	15	66 ± 13	28[x]	20
Ind.+Propantheline	10	15+20	48 ± 10	21[x]	20
Ind.+Gastrixon	10	15+20	57 ± 15	25[x]	10
Ind.+Zolimidine	10	15+100	45 ± 15	19[x]	-
Ind.+Cimetidine	9	15+150	47 ± 10	20[x]	10
Ind.+Ranitidine	10	15+50	100 ± 20	43[x]	-

$x_p < 0.01$ compared with untreated group

TABLE 8

Inhibition of Indomethacin-induced ulceration after concurrent administration of Ranitidine and Sodium-Salicylate

Treatment	*n*	*Dose mg./kg. p.o.*	*Tensile strength of s.intestine, 48 hours after treat. in mmHg*
Untreated	30	-	231 ± 5
Ranitidine (Ran.)	9	25	225 ± 8
Indomethacin (Ind.)	26	10	111 ± 10
Ind. + Ran.	9	10 + 25	145 ± 18
Ind. + Ran. + Na-Salicylate	10	10 + 25 + 100	219 ± 5[x]

$x_p < 0.01$ compared with Ind. group

TABLE 9

Inhibition of intestinal ulceration induced by a 15 mg.kg. p.o. dose of indomethacin by concurrent administration of sodium-salicylate and various anti-ulcer agents

Treatment	*n*	*Dose mg./kg p.o.*	*Tensile strength of s.intestine, 72 hours after treat., in mmHg*	*Resistance of intestinal wall in % of untreated value*	*Mortality in percent*
untreated (normal)	30	-	231 ± 5	100	-
Indomethacin (Ind.)	26	15	66 ± 10^{x}	28^{x}	20
Ind.+Propantheline (Prop.)	10	15+20	48 ± 10^{x}	21^{x}	20
Ind.+(Prop.+Na-Salic.)	10	15+(20+100)	211 ± 6^{xx}	91^{xx}	-
Ind.+Gastrixon (Gas.)	10	15+20	57 ± 15^{x}	25^{x}	10
Ind.+(Gas.+Na-Salic.)	10	15+(20+100)	211 ± 4^{xx}	96^{xx}	-
Ind.+Zolimidine (Zol.)	10	15+100	45 ± 13^{x}	19^{x}	-
Ind.+(Zol.+Na-Salic.)	10	15+(100+100)	207 ± 11^{xx}	89^{xx}	-

x_p 0.01 compared with the untreated group
xx_p 0.01 compared with indomethacin

The data set forth in Tables 1 - 2 show that the optimal ratio between cimetidine and sodium salicylate was 2:1.

In Figure 1 the time course of the intestinal ulceration induced by a 10 mg./kg. dose of indomethacin is illustrated.

Table 3 shows that a 2:1 combination of cimetidine and Na-Salicylate has a dose-dependent cytoprotective effect against abs.alcohol-induced stomach necrosis while cimetidine is not cytoprotective.

As set forth in Table 4 the intestinal toxicity of indomethacin was markedly apparent after repeated treatment on three consecutive days (3×10 mg./kg. p.o.) and the mortality was found to be 30 percent on the fourth day. Concurrent administration of 3×100 mg./kg. cimetidine p.o. resulted in a greater intestinal toxicity (mortality 50 %). Concurrent administration of 3×(100+50) mg./kg. of cimetidine and Na-Salicylate (2:1) p.o. results in an absolute blockade of intestinal toxicity.

One of the most important factors, the gastric acid secretion has been investigated in detail by using Shay-rats. The results are summarized in Tables 5 and 6. Both cimetidine and the combination of cimetidine and Na-Salicylate (2:1) have dose dependent inhibitory effect on the gastric acid secretion. The ED_{50} values for cimetidine and the combination of cimetidine and Na-Salicylate (2:1) were 54.4 mg./kg. i.p. and 35.6 mg./kg. i.p., respectively. The 35.6 mg. of the combination of cimetidine and Na-Salicylate (2:1) contained 23.8 mg. of cimetidine and 11.8 mg. of sodium salicylate. In combination a dose of cimetidine 56% less than that of cimetidine alone produced the same (50%) gastric acid secretion. Sodium salicylate alone was actually ineffective as a gastric acid inhibitor. The results were similar in case of intraperitoneal and oral treatment, respectively. The results show that a *synergism* exists between cimetidine and salicylate, as to the inhibition of gastric acid secretion.

From Table 7 it appears that the concurrent administration of the tested anti-ulcer compounds cannot block the indomethacin-induced fatal intestinal ulceration.

According to the data in Table 8 a combination of ranitidine with sodium salicylate (25+100 mg./kg.) results in a total inhibition of intestinal ulceration induced by a 15 mg./kg. p.o. dose of indomethacin.

The results obtained with combinations of various further anti-ulcer compounds and of sodium salicylate are shown in Table 9. It can be seen that while the anti-ulcer compounds listed in Table 7 alone are ineffective, in a combination with the cytoprotective sodium salicylate they can effectively block the intestinal ulceration induced with indomethacin.

According to a preferred embodiment of the invention a combination of 200 mg. cimetidine and 100 mg. sodium salicylate is used in one tablet. Instead of sodium salicylate salicylic acid or lithium salicylate can equally be used.

The pharmaceutical compositions according to the invention can be administered orally, rectally and/or parenterally, in a single daily dose or in several smaller doses. For oral administration the compositions are generally formulated as tablets, preferably coated tablets, dragées or capsules. The oral formulations according to the invention generally do not contain any excipient but, if desired, excipients like lactose or starch can also be employed. As a binding material for example gelatine, sodium carboxymethyl cellulose, methyl cellulose, polyvinylpyrrolidone or starch gum can be used. As a disintegrating agent preferably potato starch or microcrystalline cellulose are added into the compositions but ultraamylopectin or formaldehyde caseine, etc. can also be employed. As a lubricant and anti-adhesive talc, colloidal silicic acid, stearine, calcium or magnesium stearate, etc. can be used.

Such tablets may be prepared by the conventional techniques of the pharmaceutical industry, e.g. by

granulation and subsequent pressing. Thus the mixture of active ingredients and fillers and optionally a part of the disintegrating substances may be granulated with an aqueous, alcoholic or aqueous-alcoholic solution of the binding agents in a suitable apparatus and the granules obtained dried. The dry granulate may then be mixed with the further additives, e.g. disintegrating, anti-adhesive agents and lubricants, and the mixture pressed into tablets. If desired, to facilitate administration the tablets are grooved. The tablets can be coated with a gastric acid resistant film, e.g. shellac, cellulose acetate phthalate or Eudragit-L using an alcoholic, preferably isopropanolic solution of the film-forming materials. The tablets can be prepared from a mixture of the active ingredients and additives directly by pressing, and the tablets obtained can be coated with an intestino-solvent film layer.

Degées can be prepared by using various protecting, flavouring agents and pigments conventionally used in the preparation of pharmaceuticals, e.g. sugar, cellulose derivatives (methyl or ethyl cellulose, carboxymethyl cellulose sodium, etc.), polyvinylpyrrolidone, calcium phosphate, calcium carbonate, food-pigments, food-colour shellacs, iron oxide pigments, aroma substances, etc.

Capsules can for example be prepared by filling a mixture of the active ingredients and additives into a hard gelatine capsule.

For rectal administration suppositories may be prepared. As a carrier vegetable fats, e.g. hardened vegetable oils or triglycerides of fatty acids having 12 to 17 carbon atoms, preferably Witepsol are employed. The active ingredients are preferably homogeneouslydistributed in the melted mass of the carriers and suppositories are prepared therefrom by moulding.

For parenteral administration injectable preparations are prepared. The active ingredients may be dissolved in water or organic solvents, optionally in the presence of mediators, e.g. polyoxyethylene sorbitan monolaurate, monooleate or monostearate (Tween-20, Tween-60 and Tween-80, respectively,). As an organic solvent for example lower aliphatic alcohols or glycol ethers, preferably ethyleneglycol monoethyl ether, can be employed, optionally in admixture with water. The injectable solutions may contain also various auxiliary agents, such as preservatives, e.g. benzyl alcohol, *p*-hydroxybenzoic acid methyl and/or propyl ester, phenylmercuriborate or benzalconium chloride, or antioxidants, such as sodium pyrosulfate, ascorbic acid, tocopherol and optionally complexing agents to bind trace metals, e.g. ethylenediamine tetraacetic acid, and pH-adjusting and buffer materials, and optionally local anaesthetics, e.g. lidocaine.

The injectable solutions according to the invention are preferably filtered prior to filling into ampoules and are then subjected to sterilization.

The invention will further be illustrated by the following specific Examples which are for illustration only and not limitation of our invention.

Example 1

Cimetidine-sodium salicylate tablets

cimetidine	200 mg.
sodium salicylate	100 mg.
magnesium stearate	3 mg.
polyvinylpyrrolidone	8 mg.
talc	12 mg.
potato starch	27 mg.

From the materials listed above 350 mg. tablets are prepared by wet granulation and moulding. Essentially the same activity is obtained if in the above composition sodium salicylate is replaced by an equivalent amount of another alkali metal salicylate, e.g. lithium salicylate.

Examples 2 to 16

In the following Examples 2-16, tablets are prepared as in Example 1 except the active components and ingredients are present in the amounts specified below. The manufacturing procedure is the same as in Example 1. is the same as in Example 1.

Example 2

ranitidine	50 mg.
sodium salicylate	100 mg.
potato starch	8 mg.
magnesium stearate	1 mg.
polyvinylpyrrolidone	3 mg.
talc	3 mg.

Example 3

propantheline	15 mg.
sodium salicylate	75 mg.
magnesium stearate	2 mg.
potato starch	8 mg.
polyvinylpyrrolidone	2.5 mg.
talc	2.5 mg.

Example 4

gastrixone	2 mg.
sodium salicylate	25 mg.
magnesium stearate	1 mg.
potato starch	1 mg.
polyvinylpyrrolidone	0.5 mg.
talc	0.5 mg.

Example 5

zolimidine	200 mg.
sodium salicylate	100 mg.
magnesium stearate	3 mg.
polyvinylpyrrolidone	8 mg.
talc	12 mg.
potato starch	27 mg.

Example 6

cimetidine	200 mg.
sodium salicylate	100 mg.
indomethacin	20 mg.
magnesium stearate	3 mg.
polyvinylpyrrolidone	8 mg.
talc	12 mg.
potato starch	27 mg.

Example 7

cimetidine	200 mg.
sodium salicylate	100 mg.
naproxen	200 mg.
magnesium stearate	5 mg.
polyvinylpyrrolidone	3 mg.
potato starch	37 mg.
talc	15 mg.

Example 8

cimetidine	200 mg.
sodium salicylate	100 mg.
phenylbutazone	100 mg.
potato starch	40 mg.
talc	12 mg.
polyvinylpyrrolidone	12 mg.
magnesium stearate	4 mg.

Example 9

cimetidine	200 mg.
sodium salicylate	100 mg.
aspirin	200 mg.
potato starch	40 mg.
talc	20 mg.
polyvinylpyrrolidone	15 mg.
magnesium stearate	5 mg.

Example 10

cimetidine	200 mg.
sodium salicylate	100 mg.
niflumic acid	200 mg.
potato starch	40 mg.
talc	20 mg.
polyvinylpyrrolidone	15 mg.
magnesium stearate	5 mg.

Example 11

ranitidine	50 mg.
sodium salicylate	100 mg.
indomethacin	20 mg.
potato starch	15 mg.
polyvinylpyrrolidone	6 mg.
talc	6 mg.
magnesium stearate	3 mg.

Example 12

ranitidine	50 mg.
sodium salicylate	100 mg.
naproxen	150 mg.
potato starch	25 mg.
talc	10 mg.
polyvinylpyrrolidone	10 mg.
magnesium stearate	5 mg.

Example 13

ranitidine	50 mg.
sodium salicylate	100 mg.
phenylbutazone	100 mg.
potato starch	14 mg.
talc	6 mg.
polyvinylpyrrolidone	8 mg.
magnesium	2 mg.

Example 14

ranitidine	50 mg.
sodium salicylate	100 mg.
aspirin	200 mg.
potato starch	30 mg.
talc	10 mg.
polyvinylpyrrolidone	8 mg.
magnesium stearate	2 mg.

Example 15

ranitidine	50 mg.
sodium salicylate	100 mg.
niflumic acid	200 mg.
potato starch	30 mg.
talc	10 mg.
polyvinylpyrrolidone	8 mg.
magnesium stearate	2 mg.

Example 16

propantheline	15 mg.
sodium salicylate	150 mg.
indomethacin	20 mg.
potato starch	15 mg.
talc	5 mg.
polyvinylpyrrolidone	4 mg.
magnesium stearate	1 mg.

CLAIMS

1. Pharmaceutical compositions comprising, as active ingredient, 1 part by weight of an anti-ulcer agent or a salt thereof and 0.1 to 10 parts by weight of salicylic acid or an alkali metal salt thereof.

2. Compositions as claimed in claim 1 further including, as an active ingredient, 0.01 to 1 part by weight of a non-steroidal antiinflammatory agent.

3. A composition as claimed in claim 2 wherein the non-steroidal antiinflammatory agent comprises indomethacin, naproxen, phenylbutazone, acetyl-salicylic acid or niflumic acid.

4. Compositions as claimed in any preceding claim wherein the anti-ulcer agent comprises cimetidine, ranitidine, propantheline, gastrixone or zolimidine.

5. Pharmaceutical compositions comprising 0.1 to 1 part by weight of sodium salicylate and 1 part by weight of cimetidine in combination with one or more carriers and/or other additives.

6. Pharmaceutical compositions comprising 0.1 to 1 parts by weight of sodium salicyate, 0.01 to 1 part by weight of Indomethacin and 1 part by weight of cimetidine, in combination with one or more carriers and/or other additives.

7. Pharmaceutical compositions comprising 0.1 to 10 parts by weight of sodium salicylate and 1 part by weight of rantidine, in combination with one or more carriers and/or other additives.

8. Compositions as claimed in any preceding claim in which the total active ingredient concentration constitutes from 10 to 90% by weight of the total weight of the composition, the remainder consisting of one or more carriers and/or other additives.

9. Pharmaceutical compositions as claimed in claim 1 or claim 2 substantially as herein described.

10. Pharmaceutical compositions substantially as herein described in any one of Examples 1 to 16.

11. A process for the preparation of a pharmaceutical composition which comprises mixing 0.1 to 10 parts by weight of salicylic acid or an alkali metal salt thereof with 1 part by weight of an anti-ulcer agent or a salt thereof optionally together with 0.01 to 1 part by weight of a non-steroidal antiinflammatory agent and/or with one or more carriers and/or other additives.

12. A process as claimed in claim 11 wherein the anti-ulcer agent is cimetidine, ranitidine, propantheline, gastrixone or zolimidine and the optional non-steroidal antiinflammatory agent is indomethacin, naproxen, phenylbutazone, acetyl-salicylic acid or niflumic acid or a salt thereof.

13. A process as claimed in claim 12 wherein 0.1 to 1 part by weight of sodium salicylate is mixed with 1 part by weight of cimetidine.

14. A process as claimed in claim 12 wherein 0.1 to 1 part by weight of sodium salicylate is mixed with 0.01 to 1 part by weight of indomethacin and 1 part by weight of cimetidine.

15. A process as claimed in claim 12 wherein 0.1 to 10 parts by weight of sodium salicylate are mixed with 1 part by weight of ranitidine.

16. A process as claimed in claim 11 substantially as herein described.

17. A process as claimed in claim 11 substantially as herein described in any one of Examples 1 to 16.

18. Pharamaceutical compositions whenever prepared by a process as claimed in any one of claims 11 to 17.

19. A pharmaceutical product comprising a first container containing salicylic acid or an alkali metal salt thereof and a second container containing an anti-ulcer agent or a salt thereof in association with written or printed directions to administer the contents of the first and second containers concurrently in an amount of 0.01 to 10 parts by weight of salicylic acid or salt thereof to 1 part by weight of anti-ulcer agent or salt thereof.

20. A product as claimed in claim 19 further including a non-steroidal antiinflammatory agent and wherein the directions indicate that the non-steroidal antiinflammatory agent be administered concurrently with the contents of the first and second containers in an amount of 0.01 to 1 part by weight of non-steroidal antiinflammatory agent to 1 part by weight of anti-ulcer agent or salt thereof.

21. Each and every novel method, process, composition and product herein disclosed.

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